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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/647,067
Filing Date: September 25, 2000
Appellant(s): HSUEH ET AL.

Paula A. Borden
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 21 May 2004 (hereinafter called the Brief).

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct. The Examiner respectfully disagrees with Appellant's conclusion that the claimed nucleic acid sequences and polypeptide are involved in a number of functions, such as drug screening for agonists and antagonists and in the neutralization of the action of an endogenous ligand, for reasons of record and re-stated herein.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1, 2, 4, 7-11, and 18-20 stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,194,596	Tischer et al.	03-1993
5,350,836	Kopchick et al.	09-1994

Benjamin et al. Development 125: 1591-1598, 1998.

Bork, A. Genome Res 10: 398-400, 2000.

Bork et al. Trends in Genetics. 12(10): 425-427, 1996.

Brenner, S.E. Trends in Genetics 15(4): 132-133, 1999.

Doerks et al. Trends in Genetics 14(6): 248-250, 1998.

Hsu et al. Science 295 : 671-674, 2002.

Hsu et al. Molec Endocrinol 14(8) : 1257-1271, 2000.

Massague et al. Cell 49: 437-438, 1987.

Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction, pg 492-495, 1994.

Pauwels et al. Molec Neurobiol 17 : 109-135, 1998.

Pilbeam et al. Bone 14: 717-720, 1993.

Skolnick et al. Trends in Biotech 18(1): 34-39, 2000.

Smith et al. Nature Biotech 15: 1222-1223, 1997.

Spiegel et al. Annu Rev Physiol 58 : 143-170.

Vukicevic et al. Proc Natl Acad Sci USA 93: 9021-9026, 1996.

Wells, J.A. Biochemistry 29 (37): 8509-8517, 1990.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections-35 USC § 101

Claims 1, 2, 4, 7-11, and 18-20 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well-established utility and must undergo extensive experimentation. The basis for this rejection is set forth in the previous Office Actions (06 November 2002 and 23 April 2003) and is also fully set forth below.

Claims 1-2, 4, 7-11, and 18-20 are directed to an isolated nucleic acid encoding a mammalian leucine-rich repeat-containing G-protein coupled receptor 7 (LGR7) protein, wherein the LGR7 protein comprises an amino acid sequence having at least 80% amino acid sequence identity to the sequence set forth in SEQ ID NO: 8. The claims also recite an isolated nucleic acid wherein the nucleotide sequence has the sequence of SEQ ID NO: 7. Claim 7 recites an isolated nucleic acid that hybridizes under stringent conditions at 50°C or higher in a solution of 15mM sodium chloride, 1.5 mM sodium citrate to a nucleic acid having the nucleotide sequence set forth in SEQ ID NO: 7. Claims 8-10 recite an expression cassette, a host cell, and a method of producing a mammalian protein. Claim 11 is directed to a purified polypeptide composition comprising a mammalian LGR7 protein or fragment thereof, wherein the LGR7 protein is at least about 80% and wherein the LGR7 protein comprises an amino acid sequence having at least 80% amino acid sequence identity to the sequence set forth in SEQ ID NO: 8. Claim 18 is directed to a method of screening a sample for the presence of a ligand for a LGR7 receptor. Additionally, claim 19 recites that the LGR7 protein comprises an amino acid

sequence having at least 90% amino acid sequence identity to the sequence set forth in SEQ ID NO: 8. Claim 20 recites that the LGR7 protein binds a hormone.

The specification of the instant application asserts that the LGR7 polynucleotides and polypeptides share structural similarity with other known G protein-coupled receptors (GPCRs), such as leutinizing hormone (LH) receptor, follicle stimulating hormone (FSH) receptor, and thyrotropin (TSH) receptor (pg 3, lines 26-31 through pg 4, line 1). However, the assertion that the disclosed LGR7 polypeptides and polynucleotides have biological activities similar to known GPCR family members with large extracellular leucine-rich repeat regions cannot be accepted in the absence of supporting evidence, because the relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other

members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only

about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Although the specification also teaches that the LGR7 polynucleotide may be useful for producing LGR7 polypeptides, for drug screening of agonists and antagonists, and for neutralizing the action of an endogenous ligand, these asserted utilities are credible, but not specific or substantial. The asserted utilities of identification of a ligand, screening for agonists and antagonists, and generation of functional binding proteins can be performed with any polypeptide. The specification also discloses nothing specific or substantial about the ligands, agonists/antagonists, and binding proteins that are identified by these methods. Since these asserted utilities are also not present in mature form, so that they could be readily used in a real world sense, the asserted utilities are not substantial.

Additionally, the specification does not disclose any methods or working examples that demonstrate the polynucleotide and polypeptide of the instant application exhibit any activity and the skilled artisan would not be able to categorize the polynucleotide and polypeptide of the instant application as a GPCR (or a GPCR with extracellular leucine-rich repeat regions). The specification of the instant application does not even disclose the location of LGR7's transmembrane domains, extracellular domain (ectodomain), intracellular loops, extracellular loops, etc. It is clear from the instant specification that the polypeptide described therein is what

is termed an "orphan protein" in the art. This is a protein whose cDNA has been isolated because of its similarity to known proteins. There is little doubt that, after complete characterization, this DNA and protein, may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to a nucleic acid encoding a polypeptide which has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as LGR7, the instant invention is incomplete. In the absence of knowledge of the natural substrate or biological significance of this protein, there is no immediately obvious patentable use for it. Since the instant specification does not disclose a "real world" use for LGR7 encoded by the claimed nucleic acid molecule

then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

35 U.S.C § 112, first paragraph

Enablement

Claims 1, 2, 4, 7-11, and 18-20 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth in the previous Office Actions (06 November 2002 and 23 April 2003) and is also fully set forth below.

Furthermore, claims 1, 7-11, and 18-20 are rejected under 35 U.S.C. § 112, first paragraph, because the specification of the instant application does not provide evidence to demonstrate that a skilled artisan would know how to make and use the LGR7 nucleic acid fragments and variants comprising an isolated nucleic acid encoding a mammalian LGR7 protein, wherein the LGR7 protein comprises an amino acid sequence having at least 80% or at least 90% amino acid sequence identity to the sequence set forth in SEQ ID NO: 8. The specification also does not provide evidence to demonstrate that a skilled artisan would know how to make and use fragments and variants of LGR7 that have at least 80% amino acid sequence identity to the sequence set forth in SEQ ID NO: 8. It is noted that claims 2 and 4 were included in this rejection in the previous Office Actions. However, upon further consideration, the enablement issue regarding variants does not apply to claims 2 and 4.

The specification teaches that the sequence of the LGR7 gene "may be mutated in various ways known in the art to generate targeted changes in promoter strength, sequence of the encoded protein, etc. (pg 8, lines 11-13). The specification also discloses that the sequence changes may be substitutions, insertions, deletions, or a combination thereof (pg 8, lines 17-18). However, the specification also does not teach LGR7 nucleic acid variants or polypeptide variants. Further, the specification does not teach any functional or structural characteristics of the variants or fragments of the nucleic acid of SEQ ID NO: 7 or the polypeptide of SEQ ID NO: 8.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Related literature, such as Spiegel (Annual Rev. Physiol. 58:143-170, 1995) and Pauwels et al. (Molec. Neurobiol. 17(1-3): 109-135, 1998) discuss gain-of-function and loss-of-function mutations in G protein-coupled receptors that cause a wide spectrum of hereditary and somatic disorders and diseases. For

example, the ***single*** mutation of a lysine residue to a glutamate residue at position 296 in the rhodopsin receptor results in constitutive activation of that receptor and autosomal dominant retinitis pigmentosa (see Pauwels et al., pg 122, table 3). The single mutation of an aspartate residue to a glycine residue at position 578 in the LH receptor results in a gain-of-function mutation that causes the autosomal dominant genetic disease, familial male precocious puberty (Spiegel, pg 156, 2nd full paragraph). However, Appellant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins (pg 9-11), this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations and also embrace a broad class of structural fragments and variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Written Description

Claims 1, 7-11, and 18-20 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth in the previous Office Actions (06 November 2002 and 23 April 2003) and is also fully set forth below. It is noted that claims 2 and 4 were included in this rejection in the previous Office Actions. However, upon further consideration, the rejection of claims 2 and 4 under 35 U.S.C. § 112, first paragraph, written description is withdrawn.

The specification teaches that the sequence of the LGR7 gene "may be mutated in various ways known in the art to generate targeted changes in promoter strength, sequence of the

encoded protein, etc. (pg 8, lines 11-13). The specification also discloses that the sequence changes may be substitutions, insertions, deletions, or a combination thereof (pg 8, lines 17-18). However, the specification does not teach functional or structural characteristics of the nucleic acid and polypeptide in the context of a cell or organism. Appellant has not provided evidence to demonstrate that the skilled artisan would be able to envision the detailed structure of the infinite number of polynucleotides and polypeptides recited in the claims. The description of two LGR7 polynucleotides and polypeptides (SEQ ID NOs: 6, 8) in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all mutants, derivatives, and fragments of the nucleic acid sequence that encodes an amino acid sequence having at least 80% amino acid sequence identity of SEQ ID NO: 8 or all mutants, derivatives, and fragments of amino acid sequences of SEQ ID NO: 8. The instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the claimed genus of nucleic acid molecules and polypeptides. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Furthermore, the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed nucleic acid molecules or polypeptides as being identical to those instantly claimed. Therefore, only an isolated nucleic acid molecule consisting of the nucleotide sequence of SEQ ID NO: 7 and an amino acid sequence consisting of SEQ ID NO: 8, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Furthermore, the broad brush discussion of making or screening for fragments at pg 9-11 of the specification does not constitute a disclosure of a representative number of members. No such fragments were made or shown to have activity. Only one member, LGR7 of SEQ ID NO: 6 and 8, was disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed derivatives.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids and polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid molecules and polypeptide are required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to

lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated nucleic acid comprising the nucleotide sequence consisting of SEQ ID NO: 7 or a nucleotide sequence encoding the LGR7 protein set forth in SEQ ID NO: 8 and a purified polypeptide composition consisting of an amino acid sequence set forth in SEQ ID NO: 8, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Appellant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

(11) Response to Argument

Utility requirement of 35 USC § 101

At pages 9-11 and 19-20 of the Brief, Appellant summarizes the Utility Examination Guidelines and MPEP § 2107 on the utility requirement. The essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility or well-established utility, as will be explained more fully below.

Appellant asserts at the bottom of pg 10 through pg 11 and at the bottom of pg 14 of the Brief that the facts of the present application are similar to those of the hypothetical scenario described in Example 10 of the Utility Guidelines, wherein the analysis determined that the application did indeed provide the requisite well-established utility. Appellant states that the LGR7 nucleic acids and encoded polypeptides are structurally similar to a small, well-known group of GPR that binds hormones, e.g., the TSH receptor, the LH receptor, and the FSH

receptor. Appellant argues that peptide hormone receptors have a well-established use in the art and that based on the disclosed close structural similarity of LGR7 to known peptide hormone-binding GPCR, LGR7 also has a well-established utility. However, Example 10 is inapposite to the facts of the instant case. The polynucleotide sequence in Example 10 of the Utility Guidelines has high homology to DNA ligase encoding nucleic acids. In this example, DNA ligases have a well-established utility in the art based on this class of protein's ability to ligate DNA. Also, the literature discloses many DNA ligases which have been fully characterized at the structural and functional levels. However, the polynucleotide and polypeptide of the instant application are not supported by a specific and asserted utility or a well established utility although Appellant asserts that the polypeptide of SEQ ID NO: 8 encoded by the claimed polynucleotide of SEQ ID NO: 7 is homologous to the TSH receptor, LH receptor, and FSH receptor. A specific function of the LGR7 polypeptide of SEQ ID NO: 8 of the instant application is not demonstrated. Additionally, according to the Examiner's sequence search of September 5, 2002, the claimed polypeptide of SEQ ID NO: 8 of the instant application has only 13.2% or less overall sequence similarity to the TSH receptor (TSHR), LH receptor (LHR), or FSH receptor (FSHR) (please see attached sequence alignment hits summary of Appendix A). Hsu 2000 also teaches that LGR7 only shares about 24% identity with LHR, FSHR, and TSHR (Molec Endocrinol 14(8): 1257-1271, 200; pg 1258; col 2, paragraph 2). It is also noted that the binding of LH, FSH, and TSH to their respective receptors initiates different physiological responses. Furthermore, the ligand for LGR7 is not disclosed in the instant specification, nor is it known what physiological response is triggered by LGR7 activation. Therefore, there is little doubt that, after complete characterization, the DNA and protein of the instant application, may

be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete.

At the top of pg 8 and at pg 12 of the Brief, Appellant argues that the instant specification teaches that the claimed nucleic acids are useful for producing LGR7 polypeptides, which polypeptides are hormone receptors, and are useful for screening for ligands, and for the generation of soluble binding proteins for the neutralization of the action of an endogenous ligand. Appellant's arguments have been fully considered but are not found to be persuasive. The asserted utilities put forth by Appellant and the specification of the instant application are credible, but not specific or substantial. The asserted utilities of producing LGR7 polypeptides, identification of a ligand, screening for agonists and antagonists, and generation of functional binding proteins can be performed with any polypeptide. The specification also discloses nothing specific or substantial about the ligands, agonists/antagonists, and binding proteins that are identified by these methods. Substantial further research is required to determine the usefulness of ligands, agonists, antagonists, and binding proteins isolated in this manner. Since these asserted utilities are also not present in mature form, so that they could be readily used in a real world sense, the asserted utilities are not substantial.

At the bottom of pg 12 through pg 13 of the Brief, Appellant contends that the LGR7 disclosed in the instant application includes, in addition to the 7 transmembrane structure typical of other GPCR, a leucine-rich extracellular domain at the amino terminus of the protein (or ectodomain) (pg 3, line 30 though pg 4, line 1 of the specification). Appellant argues that the ectodomain of the LGR proteins is over 300 amino acids in length; the leucine rich repeat portion

of the ectodomain is approximately 200 amino acids in length; and the 7 transmembrane region is approximately 250 amino acids in length. Appellant refers to Figure 6 and Exhibits 2-4. Appellant indicates that apart from the LGR-type GPCR, no other GPCR has such an ectodomain. Appellant states at the bottom of pg 13 of the Brief that GPCR typically do not have an amino-terminal ectodomain that can be expressed as soluble proteins and used to neutralize the activity of an endogenous hormone ligand. Appellant contends that this asserted utility is specific to LGR-type GPCR. Appellant also states that fewer than 10 mammalian LGR-type GPCR had been identified as of the priority date of the instant application.

Appellant's arguments have been fully considered but are not found to be persuasive. Although the specification of the instant application discloses that LGR7 contains a leucine-rich extracellular domain (or ectodomain), the specification does not teach the location of the ectodomain in LGR7 or how large it is. Additionally, the specification does not teach the size or location of LGR7's transmembrane domains. Figure 6 of the specification only compares the amino acid sequences of LGR4, LGR5, LHR, FSHR, and TSHR and identifies various domains. Figure 6 of the instant specification does not teach any of information about LGR7 of SEQ ID NO: 8. Exhibits 2-3 show amino acid sequence alignments between LGR7 and LHR and TSHR. Exhibit 4 shows amino acid sequence alignments between LGR7, LGR8, and TSHR as well as various domains. (It is noted that LGR8 was not disclosed in the instant specification or the prior art at the time the instant application as filed.) Furthermore, although Appellant argues that the asserted utility of an amino-terminal ectodomain that can be expressed as soluble proteins and used to neutralize the activity of an endogenous hormone ligand is specific to LGR-type GPCR, this asserted utility is not specific or substantial. The specification discloses nothing specific or

substantial about LGR7's amino terminal ectodomain or LGR7's hormone ligand. Since these asserted utilities are not present in mature form, so that they could be readily used in a real world sense, the asserted utilities are not substantial. Also, according to Appellant the stanford website only indicates that fewer than 10 mammalian "LGR-type" GPCR had been identified as of the priority date of the instant application. However, the key issue at dispute is not a matter of whether the present nucleic acid encodes a LGR-type GPCR; rather, it is a matter of whether the present nucleic acid encodes a GPCR with defined biological functions; it is a matter of whether the presently claimed nucleic acid sequence and polypeptide have a patentable utility. Even the sequence analysis can place a GPCR into the GPCR family; such an assignment does not render a specific biological function and thus a patentable utility to the GPCR, since there is no single well-established utility for the GPCR family due to the great diversity in structures and functions of the GPCR family and the functions of a GPCR has to be determined experimentally, as noted above.

At the bottom of pg 13 though pg 14 and the top of pg 21 of the Brief, Appellant indicates that LGR-type GPCR have an overall structure that is very similar to LHR, FSHR, and TSHR and points to Exhibits 1-4. Appellant states that LHR, FSHR, and TSHR are hormone receptors and the relationship between LGR-type GPCR and other GPCR is illustrated in Figure 3 of Hsu et al. 2000 (Molec Endocrinol 14: 1257-1271, 2000). Appellant asserts that the analysis of LGR7 was conducted based on its structural similarity to human LHR, FSHR, and TSHR. Appellant also argues the fact that LGR7 bears a close structural relationship to LHR and TSHR and is illustrated in the alignments of Exhibits 2-4. Appellant's arguments have been fully considered but are not found to be persuasive. Exhibits 1-4 and Figure 3 of Hsu 2000 do not

clearly indicate any strong sequence similarity between LGR7 and LHR, FSHR, TSHR, or any other putative "LGR-type" GPCR. Figure 6 of the instant specification only compares the amino acid sequences of LGR4, LGR5, LHR, FSHR, and TSHR and identifies various domains. Figure 6 of the instant specification does not teach any of information about the claimed LGR7 nucleic acid molecule of SEQ ID NO: 7 or LGR7 polypeptide of SEQ ID NO: 8. Exhibit 1 indicates the functional domains in various receptors, including LGR7. Exhibits 2-3 show amino acid sequence alignments between LGR7 and LHR and TSHR. Exhibit 4 shows amino acid sequence alignments between LGR7, LGR8, and TSHR as well as various domains. However, there is no disclosure in the specification of the location or size of any putative domains in the LGR7 polypeptide. There is also no disclosure in the specification or prior art of the specific structural and functional similarities between LGR7 and LHR, FSHR, TSHR, or other LGR-type GPCR family members. Hsu 2000 teaches that LGR7 only shares about 24% identity with LHR, FSHR, and TSHR (pg 1258; col 2, paragraph 2). Furthermore, as discussed above, according to the Examiner's sequence search of September 5, 2002, the LGR7 polypeptide of SEQ ID NO: 8 of the instant application has only 13.2% or less overall sequence similarity to the TSH receptor, LH receptor, or FSH receptor (please see attached sequence alignment hits summary of Appendix A).

Appellant's assertion that the disclosed LGR7 polypeptides and polynucleotides have biological activities similar to known GPCR family members with large extracellular leucine-rich repeat regions cannot be accepted in the absence of supporting evidence, because the relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S.

Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48). Finally, Spiegel (Annual Rev. Physiol. 58:143-170, 1995) and Pauwels et al. (Molec. Neurobiol. 17(1-3): 109-135, 1998) discuss gain-of-function and loss-of-function mutations in G protein-coupled receptors that cause a wide spectrum of hereditary and somatic disorders and diseases. For example, the ***single*** mutation of a lysine residue to a glutamate residue at position 296 in the rhodopsin receptor results in constitutive activation of that receptor and autosomal dominant

retinitis pigmentosa (see Pauwels et al., pg 122, table 3). The single mutation of an aspartate residue to a glycine residue at position 578 in the LH receptor results in a gain-of-function mutation that causes the autosomal dominant genetic disease, familial male precocious puberty (Spiegel, pg 156, 2nd full paragraph). However, Appellant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a

common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

At pg 15 and pg 21 of the Brief, Appellant asserts that the disclosed LGR7 polypeptide, like LHR, FSHR, and TSHR, binds a hormone, functions as a GPCR, and has signal transduction properties similar to those of LHR. Appellant submits that the fact that the instant claims are supported by a well-established utility is demonstrated in Hsu et al. 2002 (Science 295: 671-674, 2002). Appellant indicates that Hsu 2002 states LGR7 binds the hormone, relaxin, and that relaxin activates adenylate cyclase through G_s proteins upon relaxin binding. Appellant reiterates that Hsu 2002 provides further evidence that LGR7 functions as a GPCR and is a hormone receptor. At the bottom of pg 15 through the top of pg 16 of the Brief, Appellant discusses that the specification teaches the solubilized LGR7 ectodomain is useful to neutralize the activity of the endogenous hormone ligand of LGR7 (pg 21, lines 12-15). Appellant points out that Hsu 2002 states the 7BP, a soluble ectodomain of LGR7, antagonizes the action of the endogenous hormone ligand of LGR7, relaxin. Appellant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges that the asserted utilities of LGR7 being a GPCR, binding a hormone, and having signal transduction properties

are credible, but not specific or substantial. The specification of the instant application discloses nothing specific or substantial about the exact domains, functions, or signalling properties of LGR7 of SEQ ID NO: 8 that would characterize the protein as a GPCR. The specification also discloses nothing specific or substantial about the hormone ligand. The specification does not disclose the identity of relaxin as the hormone that binds LGR7.

At pg 16 of the Brief, Appellant argues that the Examiner has provided no basis in reasoning for the statement "novel biological molecules lack well-established utility and must undergo extensive experimentation". Appellant argues that the Examiner has swept the "well-established utility" question away in one sentence without any explanation of well-reasoned statements. Appellant's arguments have been fully considered but are not found to be persuasive. Specifically, a product such as a hammer, has a well-established utility in that one skilled in the construction arts could identify how it is useful without the aid or guidance of assertions of utility for the hammer. Conversely, one skilled in the biological arts cannot look at a sequence of amino acids and immediately determine how it is useful, without further structural and functional characterization and the aid or guidance of assertions of utility. Extensive experimentation is performed in the biological arts to determine the usefulness of any new protein. The regulation and sequestration of the LGR7 nucleic acid sequences and polypeptides of the instant application are not well characterized and one skilled in the art the art would not find the utility of the LGR7 nucleic acid sequences and polypeptides to be well-established, well-known or obvious or substantial. Appellant asserts that Example 10 of the Utility Guidelines indicates the exemplary DNA ligase encoding nucleic acid may be a novel biological material and be deemed to have a well-established utility. However, DNA ligases are extremely well

characterized both structurally and functionally, unlike GPCR (for example, see several of the subfamilies cited in Spiegel et al. (Ann Rev Physiol 58: 143-170, 1995; pg 149-162)). It is clear from the instant specification that the LGR7 protein described therein is what is termed an "orphan protein" in the art. This is a protein whose cDNA has been isolated because of its similarity to known proteins. There is little doubt that, after complete characterization, this DNA and protein, may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete.

At pg 17-18 of the Brief, Appellant concludes that analogous to Example 12 of the Utility Guidelines, the present application states that the extracellular domain can be solubilized and used to neutralize the activity of the endogenous ligand (hormone) (pg 11, lines 3-4; pg 21, lines 12-15). Appellant states that the LGR7 polypeptides are useful for identification of a ligand for the GPCR; for screening agonists and antagonists. Appellant discusses that LGR7 belongs to a small, distinct subset of GPCR with well-known functions and therefore, there is an asserted specific utility. At the bottom of pg 18 through the top of pg 19 of the Brief, Appellant also mentions that in contrast to the hypothetical scenario of Example 12 of the Utility Guidelines, the instant specification discloses information regarding the receptor, the endogenous ligand for the receptor, as well as a context for use of the receptor. Appellant concludes that the present application asserts a substantial utility. Appellant's arguments have been fully considered but are not found to be persuasive. The fact pattern of Example 12 of the Utility Guidelines Training Materials is similar to the fact pattern of the instant case. In Example 12, the hypothetical specification discloses that a protein is isolated, but the protein (a putative receptor) is not

characterized with regard to its biological function or any disease or body condition that is associated with it. Example 12 of the Utility Guidelines indicates that for the putative receptor, there is no well-established utility and the asserted utility is not substantial. Regarding the instant application, although the specification also teaches that the LGR7 polynucleotide may be useful for producing LGR7 polypeptides, for drug screening of agonists and antagonists, and for neutralizing the action of an endogenous ligand, these asserted utilities are credible, but not specific or substantial. The asserted utilities of identification of a ligand, screening for agonists and antagonists, and generation of functional binding proteins can be performed with any polypeptide. The specification also discloses nothing specific or substantial about the ligands, agonists/antagonists, and binding proteins that are identified by these methods. Substantial further research is required to determine the usefulness of ligands, agonists, antagonists, and binding proteins isolated in this manner. The specification of the instant application discloses nothing specific or substantial about the exact domains, functions, or signalling properties of LGR7 of SEQ ID NO: 8 that would characterize the protein as a receptor. The specification also discloses nothing specific or substantial about the hormone ligand. The ligand for LGR7 is not disclosed in the instant specification, nor is it known what physiological response is triggered by LGR7 activation. Since these asserted utilities are also not present in mature form, so that they could be readily used in a real world sense, the asserted utilities are not substantial.

Appellant contends at pg 20 of the Brief that the specification states that LGR7 binds a hormone. Appellant argues that in view of the structural similarity of LGR7 to other GPCR that share the feature of having a large ectodomain and that binds hormone ligands, the utility would have been readily apparent to one of skill in the art in view of the disclosure. Appellant states

that Exhibits 2-4 (which were previously submitted) show the position of the ectodomain of LGR7. Appellant submits that there was ample guidance in the specification that would have allowed the skilled artisan to perform the same amino acid sequence alignments as provided in Exhibits 2-4, compare such alignments with those depicted in Figure 6 as filed, and identify the position of the ectodomain in LGR7. Appellant points out that Figure 2 of Hsu 2002 provides an amino acid sequence alignment of LGR7, indicates the leucine-rich repeats that are characteristics of the ectodomain, and shows the site of the beginning of the first transmembrane domain, thereby delineating the ectodomain. Appellant argues that anyone skilled in the art, given the amino acid sequences provided in the specification, the publicly available LHR, FSHR, and TSHR amino acid sequences, and using Figure 6 as a guide, could have readily identified the ectodomain of LGR7. Appellant's arguments have been fully considered but are not found to be persuasive. Although the specification of the instant application discloses that LGR7 contains a leucine-rich extracellular domain (or ectodomain), the specification does not teach the location of the ectodomain in LGR7 or how large it is. Additionally, the specification does not teach the size or location of LGR7's transmembrane domains. Figure 6 of the specification only compares the amino acid sequences of LGR4, LGR5, LHR, FSHR, and TSHR and identifies various domains. Figure 6 of the instant specification does not teach any of information about LGR7 of SEQ ID NO: 8. Exhibits 2-3 show amino acid sequence alignments between LGR7 and LHR and TSHR. Exhibit 4 shows amino acid sequence alignments between LGR7, LGR8, and TSHR as well as various domains. However, there is no disclosure in the specification of the instant application or the prior art of the structural and functional similarities between LGR7 and LHR, TSHR, FSHR, or other "LGR-type" GPCR. Exhibits 2-4 do not clearly indicate any strong

sequence similarity between LGR7 and LHR and TSHR. For example, Hsu 2000 teaches that LGR7 only shares about 24% identity with LHR, FSHR, and TSHR (pg 1258; col 2, paragraph 2) and according to the Examiner's sequence search of September 5, 2002, the LGR7 polypeptide of SEQ ID NO: 8 of the instant application has only 13.2% or less overall sequence similarity to TSHR, LHR, or FSHR (please see attached sequence alignment hits summary of Appendix A). It is also noted that the binding of LH, FSH, and TSH to their respective receptors initiates different physiological responses. Therefore, one skilled in the art would not have readily identified the ectodomain of LGR7 or even categorized the claimed LGR7 protein of SEQ ID NO: 8 as a GPCR in the glycoprotein subfamily with LHR, FSHR, and TSHR. The specification discloses nothing specific or substantial about LGR7's amino terminal ectodomain or LGR7's hormone ligand. The ligand for LGR7 is not disclosed in the instant specification, nor is it known what physiological response is triggered by LGR7 activation. Since these asserted utilities are not present in mature form, so that they could be readily used in a real world sense, the asserted utilities are not substantial.

Enablement requirement of 35 U.S.C. § 112, first paragraph

As Appellant indicates at pages 8 and 22 of the Brief, a rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967).

Issues of enablement requirement regarding polynucleotide and polypeptide variants

Appellant indicates at pages 8 and 22 of the Brief that the specification teaches various polypeptide variants of LGR7 and provides the nucleotide and amino acid sequences of at least two LGR7 polypeptides. At the bottom of pg 22 through the top of pg 23 of the Brief, Appellant states that the specification discusses the structure of LGR7 and that LGR7 contains a leucine-rich repeat-containing ectodomain. Appellant argues that those skilled in the art, given the guidance in the specification, would know which fragments of LGR7 would be expected to function. Additionally, Appellant asserts that based on the alignments in Figure 6, those skilled in the art could readily determine, without undue experimentation, those amino acids of LGR7 that could be altered without changing the function of LGR7. Appellant states that the fact that those skilled in the art could readily identify amino acid residues essential for function is demonstrated in Hsu 2000, wherein point mutations were made in LGR7 that affected its function as a GPCR.

Appellant's arguments have been fully considered but are not found to be persuasive. The specification does not teach any functional or structural characteristics of the full-length LGR7 nucleic acid of SEQ ID NO: 7, the polypeptide of SEQ ID NO: 8, or variants or fragments thereof. Additionally, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-

dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Although the specification outlines art-recognized procedures for producing and screening for active muteins (pg 9-11), this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Additionally, related literature, such as Spiegel (Annual Rev. Physiol. 58:143-170, 1995) and Pauwels et al. (Molec. Neurobiol. 17(1-3): 109-135, 1998) discuss gain-of-function and loss-of-function mutations in G protein-coupled receptors that cause a wide spectrum of hereditary and somatic disorders and diseases. For example, the ***single*** mutation of a lysine residue to a glutamate residue at position 296 in the rhodopsin receptor results in constitutive activation of that receptor and autosomal dominant retinitis pigmentosa (see Pauwels et al., pg 122, table 3). The single mutation of an

aspartate residue to a glycine residue at position 578 in the LH receptor results in a gain-of-function mutation that causes the autosomal dominant genetic disease, familial male precocious puberty (Spiegel, pg 156, 2nd full paragraph). However, Appellant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Furthermore, Figure 6 of the specification only compares the amino acid sequences of LGR4, LGR5, LHR, FSHR, and TSHR and identifies various domains. Figure 6 of the instant specification does not teach any of information about LGR7 of SEQ ID NO: 8. Therefore, one skilled in the art would still not be able to readily determine, without undue experimentation, those amino acids of LGR7 that could be altered without changing the function of LGR7. Although Appellant states that the fact that those skilled in the art could readily identify amino acid residues essential for function is demonstrated in Hsu 2000 (wherein point mutations were made in LGR7 that affected its function as a GPCR), there is no disclosure in the specification of the instant application or the prior art of the structural and functional similarities between LGR7 and LHR, TSHR, FSHR, or other "LGR-type" GPCR. For example, Hsu 2000 teaches that LGR7 only shares about 24% identity with LHR, FSHR, and TSHR (pg 1258; col 2, paragraph 2) and according to the Examiner's sequence search of September 5, 2002, the LGR7 polypeptide of SEQ ID NO: 8 of the instant application has only 13.2% or less overall sequence similarity to TSHR, LHR, or FSHR (please see attached sequence alignment hits summary of Appendix A). Therefore, one skilled in the art would not have readily identified the ectodomain

transmembrane domains of LGR7 or even categorized the claimed LGR7 protein of SEQ ID NO: 8 as a GPCR in the glycoprotein subfamily with LHR, FSHR, and TSHR. Furthermore, although Hsu 2000 is able to make point mutations in LGR7 based on homology to the LH receptor and TSH receptor, Hsu 2000 also discloses that mutagenesis of conserved residues for the characterization of signaling by orphan receptors is only applicable to selective orphan GPCRs (pg 1265, col 2, last sentence). Hsu 2000 even discloses that previous studies indicated that an FSH receptor mutant equivalent to D578Y in the LH receptor does not lead to receptor activation as it does in the LH receptor (pg 1265, col 2, last sentence). Appellant has provided little or no guidance beyond the mere presentation of sequence data in the specification to enable one or ordinary skill in the art to determine, without undue experimentation, the positions in the LGR7 protein and DNA which are tolerant to change and the nature and extent of changes that can be made in these positions.

At the bottom of pg 23 of the Brief, Appellant reiterates that the amino acid sequence of LGR7 could be aligned with the amino acid sequence of other LGR-type GPCR, and amino acids could be successfully identified that altered the function, or that had no effect on the function, of LGR7. Appellant contends that those skilled in the art could identify, make, and use LGR7 variants without undue experimentation. At pg 24 of the Brief, Appellant cites MPEP § 2164.01 to emphasize that the skill level in the art is high and that practitioners in the chemical molecular biology arts frequently engage in extensive modification of reaction conditions and complex lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. At pg 25 of the Brief, Appellant contends that Hsu 2000, carrying out routine experimentation, identified amino acid residues for function of the

LGR7. Appellant also indicates that Hsu 2002 carrying out nothing more than routine experimentation, generated a soluble LGR7 ectodomain and demonstrated that a soluble extracellular domain of LGR7 functions as an antagonist to LGR7, neutralizing the action of the ligand, relaxin.

Appellant's arguments have been fully considered but are not found to be persuasive. It is noted that a specification may be enabling even though some experimentation is necessary, but the amount of experimentation, however, must not be unduly extensive (MPEP § 2164.06). In the instant case, the specification's general discussion of making and screening for variants (pg 9-11) constitutes an invitation to experiment by trial and error. Undue experimentation would be required by the skilled artisan to generate the infinite number of LGR7 nucleic acid and polypeptide fragments and variants recited in the claims and to screen them for a desired activity. Such trial and error is considered undue. Also, the specification does not teach the detailed structure of LGR7, particularly its ectodomain. A large quantity of experimentation would be required of the skilled artisan to identify amino acids that could be altered in LGR7's overall sequence based upon sequence alignments with other LGR-type GPCRs, due to the low sequence identity shared between LGR-7 and other LGR-type GPCRs, such as LHR, TSHR, FSHR (see attached Appendix A; see Hsu et al. 2000, pg 1258, col 2, paragraph 2). Therefore, based upon the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed polynucleotides to make biologically active LGR-7 and LGR7 variants without resorting

to undue experimentation to determine what the specific biological activities of the LGR-7 polypeptide and all LGR-7 variants are.

Written description

At pages 26-27 of the Brief, Appellant cites and summarizes the Written Description Guidelines. Appellant asserts at the bottom of pg 27 of the Brief that the Examiner has not reviewed the instant claims for compliance with the written description requirement in a manner consistent with the Written Description Guidelines. Appellant contends that the Examiner has merely stated that the description of two LGR7 polynucleotides and polypeptides in the specification is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides. Appellant argues that the Examiner has not presented evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. At the top of pg 28 of the Brief, Appellant asserts that the Examiner has not conducted a review of the claims from a standpoint of one skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge in the art. At the top of pg 9 and at the bottom of pg 28 of the Brief, Appellant asserts that the specification provides the nucleotide and amino acid sequences of at least two LGR7 polypeptides. Appellant submits that the specification provides a description of various fragments of LGR7 polypeptides and uses thereof.

Appellant's arguments have been fully considered but are not found to be persuasive. The skilled artisan cannot envision the detailed chemical structure of the numerous encompassed

nucleic acids and polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid molecules and polypeptide are required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Appellant has not provided evidence to demonstrate that the skilled artisan at the time the invention was filed would have been able to envision the detailed structure of the infinite number of polynucleotides and polypeptides recited in the claims. The description of two LGR7 polynucleotides and polypeptides in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all mutants, derivatives, and fragments of the nucleic acid sequence that encodes an amino acid sequence having at least 80% amino acid sequence identity of SEQ ID NO: 8 or all mutants, derivatives, and fragments of amino acid sequences of SEQ ID NO: 8. The instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the claimed genus of nucleic acid molecules and polypeptides. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Furthermore, the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed nucleic acid molecules or polypeptides as being identical to those instantly claimed.

At pg 28 of the Brief, Appellant submits that, as stated in the Written Description Guidelines, what constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Appellant argues that the Examiner failed to take into account the level of skill of those in the relevant art as of the March 26, 1998 priority date of the instant application. Appellant adds that the skill and knowledge in the art relating to protein sequence, structure, and function, was so high as of the priority date that, given the instant disclosure, those skilled in the art would immediately recognize that Appellants had in the their possession the claimed nucleic acids and polypeptides.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Appellant has not provided evidence to demonstrate that the skilled artisan at the time the invention was filed would have been able to envision the detailed structure of the infinite number of polynucleotides and polypeptides recited in the claims. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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